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Comparison of sevoflurane insufflation and intravenous ketamine use in terms of failure rate in consecutive paediatric radiotherapy sessions: a cross-over study

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ABSTRACT

Aims: Childhood cancers are often treated with radiotherapy. During radiation therapy, sedation is often required for immobilization, especially for young children and patients with mental disabilities. Our study aimed to compare the efficacy of sevoflurane insufflation and intravenous ketamine for sedation during pediatric radiotherapy.

Methods: This prospective, randomized, cross-over study was conducted between August and December 2020 on pediatric patients (1 month to 18 years) requiring sedation or general anesthesia for radiotherapy. Three hundred fifty-two repeated sessions were conducted in the study involving 18 participating patients. Two groups were categorized by session: ketamine (Group K) or sevoflurane (Group S).

Results: The study included the evaluation of 352 sessions for 18 patients. Although there was no significant difference in procedure times between Group S and Group K during the sessions ($p>0.05$), Group K showed a significantly longer discharge time, higher failure rate, and higher score sedation scale in comparison to Group S ($p<0.001$).

Discussion: During radiotherapy sessions conducted outside of the operating room for children, the use of sevoflurane sedation was found to have a lower failure rate compared to intravenous sedation.

Keywords: Nonoperating room sedation, sevoflurane, ketamine, radiotherapy, childhood malignancies

INTRODUCTION

Radiotherapy (RT) is a frequently used treatment for childhood cancers. During radiation therapy, it is necessary to immobilize children to protect healthy tissues and ensure accurate radiation targeting of pathological tissues. Immobilization during radiation therapy often requires either superficial or deep sedation, particularly for children aged 0-5 and patients with mental disabilities.

Patients undergoing RT receive sedation during daily sessions lasting one to six weeks.[1] Due to high-energy radiation, the patient must be left alone in the treatment room during RT applications. However, the anesthesia team monitors patients through cameras from outside the room to ensure their safety. When a patient wakes up during a procedure, experiences apnea due to sedation, or if there is a problem with the device or position, it takes around 30 seconds to open the door of the RT room and provide urgent intervention.[2] These reasons may cause interruptions in the procedure, leading to longer procedure times and extended sedation periods.

An ideal method for pediatric sedation should be reliable, provide an amnesic effect, reduce anxiety, and offer immobility and analgesia.[3,4] While producing these effects, it must not depress respiratory and cardiovascular reflexes. The drugs should have a short onset and duration time, and their dosage should be adjusted based on the patient's response. Side effects should be minimized.[5]

During radiation therapy, it is essential to ensure that the patient is sedated to a level where they cannot move during the procedure. This is necessary for the treatment to be effective, but ensuring that the patient's spontaneous breathing is not suppressed is also essential. Administering additional anesthetic agents during RT interruption can decrease treatment effectiveness. In addition to the RT session, early patient recovery and discharge are important considerations. Proper dose titration of anesthetic agents can be extremely challenging under such conditions, especially during lengthy procedures.[6] Different centers utilize various

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sedation and anesthesia techniques during radiation therapy for children under 4 years old.[7,8] Sedation is often achieved through the use of propofol, midazolam, remifentanil, fentanyl, and ketamine.[9,10]

Our study aimed to compare the effectiveness of two sedation methods, sevoflurane insufflation, and intravenous ketamine, during RT sessions for pediatric patients, in terms of failure rate, discharge time and acquiring an airway with assistance. The study evaluated the occurrence of adverse events such as desaturation, hypoventilation, airway spasm, bradycardia, and tachycardia in relation to the continuous completion of the RT session with immobilization. Our study secondly aimed to investigate anesthesia complications in RT patients and identify associated factors.

METHODS

The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 02.07.2020 Decision No: E1-20-884). From August to December 2020, a study was carried out at our hospital. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[11]

Study Population

We included all children between 1 month and 18 years who require sedation or general anesthesia for radiotherapy at Ankara City Hospital Radiotherapy Unit during August to December 2020. The study included 18 patients who participated in 352 repeated sessions. Patient data was collected during each session.

Children with certain medical conditions were excluded from the study, including symptomatic increased intracranial pressure, chronic nausea and vomiting, respiratory tract infections or diseases, cardiac disease, kidney or liver failure, and neurological or muscular diseases. All parents provided written informed consent.

Study Design

The study was prospective and randomized, with a cross-over design. Groups were categorized based on their session: IV ketamine (0.5 mg/kg) or sevoflurane (3%). The order in which the two different methods were applied to the 18 children in the daily sessions was determined using the closed envelope method in the first session. For the following sessions, the technique used was switched daily. Therefore, both groups consisted of 18 identical children who received either ketamine or sevoflurane sedation during sessions.

Anesthetic Management

All children received pre-anesthetic assessments and were classified based on ASA physical status classification a few days before the procedure at the hospital.

Per standard fasting guidelines, all children were kept nil per os (NPO) pre-operatively and received intravenous fluids after fasting.[12] Before being taken to the radiotherapy room, all children were administered 0,05 mg/kg of midazolam. Each child received standard intraoperative monitoring (non-invasive arterial blood pressure, heart rate, pulse oximetry, and end-tidal CO_2), and all intra-operative and postoperative events were recorded on an anesthetic record form until the patient achieved full recovery. The Pediatric Sedation Status Scale[13] was used to adjust the sedation depth to stage 2.

Group S: Sevoflurane insufflation at 8% concentration in oxygen 6lt/min began using an oxygen mask with sealed holes to prevent leakage. After loss of consciousness, we immediately reduced sevoflurane concentration to 2-3%.

Group K: The children were given a dose of 0.5 mg/kg of ketamine and oxygen 6lt/min using an oxygen mask when positioned on the radiotherapy table. After securing the child on the table, additional boluses of 0.025 mg/kg ketamine were administered if the child responded to stimulation.

Data Recorded

The patient's age, body weight, body mass index (BMI), body surface area (BSA), American Society of Anesthesiologists (ASA) physical status, and fasting time were recorded prior to RT. The duration of anesthesia, any interruptions during the procedure, use of an auxiliary airway, and incidents of nausea and vomiting were all documented and noted. Recorded complications included respiratory (apnea, airway obstruction, cough, desaturation) and cardiac (bradycardia, tachycardia, hypotension, hypertension, arrhythmia). Apnea is defined as a period of breathing interruption that lasts for more than 10 seconds or a reduction in the level of $ETCO_2$. Desaturation is defined as the level of SpO_2 below 92%, while bradycardia/hypotension and tachycardia/hypertension are defined as below and 30% above the baseline, respectively.

Any interruption during RT caused by hypotension, hypoventilation, bradycardia, desaturation, or movement was defined as a failure rate. The main objective was to compare the failure rate between the groups that received sevoflurane insufflation and ketamine. The secondary outcomes included the use of an auxiliary airway, respiratory and cardiac complications, and incidents of nausea and vomiting between the groups.

After the procedure, the patient was closely monitored in the recovery room until their Modified Steward score reached a minimum of 8.[14] The duration between the end of radiotherapy and the patient's recovery to a modified Stewart scale of 8 was noted as the "discharge time."

Sample Size Estimation

The study titled "Does sevoflurane add to outpatient procedural sedation in children? A randomized clinical trial" aimed to determine the number of patients needed for the study based on the Houpt crying scores as a reference. The required sample size is at least 18 patients with a d=0.71 effect size of 80% power and an error level of 0.05, or a total of 92 sessions with at least 46 sessions for each group.[15]

The calculation was performed using the "GPower 3.1.9.2" software package.

Statistical Analysis

Descriptive statistics provided Mean, Standard Deviation, Median, and IQR values for continuous data and number and percentage values for discrete data. The Shapiro-Wilk test was utilized to assess whether the continuous data adheres to a normal distribution. For comparing continuous data, the Mann-Whitney U test was utilized. Chi-square and Fisher's exact tests were used to compare nominal variables between groups using cross tables. The statistical software IBM SPSS version 20 from Chicago, IL, USA, was used for analysis. A significance level of $p<0.05$ was considered.

RESULTS

The study included the evaluation of 352 sessions for 18 patients. The patients' mean age was 42.17±25.09 months, ranging from 21 to 108 months old. The patients' average body surface area (BSA) was 0.63±0.15 m². Out of the total number of patients, 38.9% (7 patients) were girls, while 61.1% (11 patients) were boys (Table 1, 2).

Table 1. Characteristics of the children

n=18	Mean±SD Median (Min-Max); IQR	
Age (months)	42.17±25.09 36 (21-108); (24-51)	
Height(cm)	98.83±17.77 97 (65-145); (90-105)	
Weight (kg)	15.07±5.35 15 (8-31); (11-17)	
BSA (m²)	0.63±0.15 0.60 (0.42-1.04); (0.53-0.69)	
	n	%
Gender		
Girl	7	38.9
Boy	11	61.1

SD: Standart Deviation, IQR: Interquartile Range, BSA: Body Surface Area

Table 2. Descriptive values of sessions received by patients

n=18	Mean±SD	Median (Min-Max); (IQR)
Total number of sessions	19.56±9.75	17.5 (6-32); (11-30)

SD: Standart Deviation, IQR: Interquartile Range

There was no significant difference in processing times between Group S and Group K during the sessions ($p>0.05$).

In the comparison of groups, it was found that discharge time for Group K was significantly longer during sessions ($p<0.001$). In comparing the two groups, the failure rate in Group K was significantly higher than in Group S ($p<0.001$).

During the sessions, there was no statistically significant difference between Group S and Group K in terms of acquiring an airway with assistance ($p>0.05$). During the sessions, it was observed that there was a significant difference in the Sedation scale between Group S and Group K. The Sedation scale of Group K was significantly higher than that of Group S ($p<0.001$). In the comparison between the two groups, Group K had a significantly higher rate of nausea and vomiting after sessions than Group S ($p<0.05$) (Table 3).

Table 3. Intergroup comparison of sessions

Number of sessions, n (%)	Group S 176 (50%)		Group K 176 (50%)		p value
	Mean±SD; median (IQR)		Mean±SD; median (IQR)		
Processing Time (min)	9.16±5.91; 6 (5-13)		8.51±5.17; 7 (5-12)		0.565[b]
Discharge Time (min)	6.23±1.93; 6 (5-7)		8.04±1.98; 8 (7-9)		<0.001[b]
	n	%	n	%	
Failure rate					<0.001[c]
0	173	98.3	144	81.8	
>0	3	1.7	32	18.2	
Acquiring an airway with assistance					0.138[c]
No	164	93.2	156	88.6	
Yes	12	6.8	20	11.4	
Sedation scale					<0.001[c]
2	171	97.2	84	47.7	
3	4	2.3	65	36.9	
4	1	0.6	27	15.3	
Nause and vomiting					0.030[c]
No	176	100	170	96.6	
Yes	0	0	6	3.4	

SD: Standart deviation, IQR: Interquartile range, b: Mann Whitney U test, c: Chi-square test/Fisher's Exact Test

DISCUSSION

Our study involved 352 sessions where 18 children were sedated using crossover sevoflurane and ketamine. Sevoflurane sedation resulted in significantly lower failure rates, discharge duration, and sedation scales during the procedure.

Şimşek et al.[16] demonstrated successful use of sevoflurane sedation for non-operating room anesthesia in 187 pediatric patients while maintaining hemodynamic stability.

Choopong et al.[17] reported a significantly higher success rate in MRI with sevoflurane insufflation compared to propofol infusion.

In their study, Briggs et al.[18] compared the adverse effects of sevoflurane sedation on neonates undergoing MRI imaging. Based on their findings, they concluded that sevoflurane is an excellent sedative for both neonates and infants because of its fast induction, effective maintenance, quick recovery, and low incidence of complications.

In a study conducted by Ogurlu et al.[19] the effectiveness of different concentrations of sevoflurane for sedation during MRI imaging was compared. The results showed that administering a 1% concentration of sevoflurane through a face mask while allowing children to breathe normally is a safe and effective method of providing anesthesia without any impact on their spontaneous breathing.

In a study conducted by Montes et al.[20] sedation with sevoflurane was found to have a significantly lower total time to awakening, discharge, and including induction and procedure when compared to propofol and midazolam+ketamine during endoscopy in children. The study also found that sevoflurane had a lower complication rate than midazolam-fentanyl-ketamine and propofol.

Gomes et al.[15] compared the side effects of adding inhaled sevoflurane to a mixture of oral midazolam and ketamine in young children's dental treatment. According to the research, children who were given sevoflurane exhibited reduced levels of crying and movement in comparison to those who were given oxygen. Moreover, the study found that there was no increase in the occurrence of adverse events with sevoflurane supplementation.

As mentioned above, various non-operating room applications have compared IV anesthetic drugs and sevoflurane. The study focuses on the impact of treatment failure on the interruption of the procedure. The comparison made in the study pertains to this specific aspect of the process. In this study, consistent with previous research, it was found that sevoflurane sedation resulted in a significantly lower failure rate compared to ketamine sedation. It was found that no significant differences in cardiac and respiratory complications, as well as nausea and vomiting, between the two groups of children. Children receiving sevoflurane experienced faster recovery and shorter discharge times than the other group.

This study has a strong point that both sedation methods were used in consecutive sessions of the same patients, ensuring that there were no demographic data differences between the two groups.

Limitations

Due to the small number of patients, our study was limited in its evaluation of patients with different cancer types and frailties. As a result, we did not analyze the factors that could affect the failure rate through multivariate analysis.

CONCLUSION

We found that using sevoflurane sedation resulted in a lower failure rate compared to IV sedation in children undergoing RT sessions outside of the operating room. Sevoflurane sedation can be safely used for sedation outside of the operating room, allowing for spontaneous respiration to continue. This method has been shown to be well-tolerated by children, even those who may have a lower rate of failure during RT sessions. Additionally, this sedation method does not result in adverse side effects and leads to shorter recovery and discharge times.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 02.07.2020 Decision No: E1-20-884).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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